DiamondBlackfanAnemia.org
Daniella Maria Arturi Foundation Research For The Cure

Wrap Up of ICC 2012

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The 12th Diamond Blackfan Anemia Clinical Consensus Conference was held March 17-19th 2012 in New York City. In providing this synopsis of the meeting I thought I would turn things around a bit and begin at the end of the conference. My rationale for this is that one of the reasons the Daniella Maria Arturi Foundation sponsors the ICC meetings is to develop more effective therapies for DBA with reduced toxicities. So, I thought I would begin this meeting review with the question "Has the science of Diamond Blackfan anemia which has shown remarkable progress in the past few years translated into new therapies for DBA patients?"

To address this question, let me turn to the last session of the meeting, entitled **"Clinical Treatment and Drug Development"**.

Dr. Anu Narla (Boston) gave a talk on the effects of leucine on zebrafish and human cell lines models of DBA. The results in these models systems continues to be encouraging, as was work in a poster presented by Pekka Jaako (Sweden) on the effects of leucine in his mouse model of DBA. A poster was also presented by Dr. Dagmar Pospisilova (Czech Republic) on the results of an ongoing trial of leucine administration in a relatively small number of patients in the Czech Republic. Here, again there is some evidence of a positive effect of leucine in stimulating erythropoiesis in some of the treated patients. Questions were raised concerning the status of the proposed leucine trail here in the United States. Dr. Vlachos indicated that they are still working through some FDA regulatory issues that will need to be resolved before the trail can begin. Let's hope these issues can be resolved quickly.

Dr. Carol Mercer (Cincinnati) gave a talk on using a small molecule inhibitor of p53 to rescue some of the phenotypes in their mouse model of DBA. While many are concerned of the potential side effects of using an inhibitor of arguably the most important tumor suppressor protein in the human body as a potential treatment for DBA, these studies represent an important proof of principle which may someday allow more targeted therapies that block contributes made by p53 activation to DBA pathogenesis without increasing cancer risk.

A more outside the box treatment for DBA was presented by Dr. Johnson Liu (New York). He has opened a clinical trial for adult DBA patients using a drug initially developed for osteoporosis which had the unanticipated side effect of stimulating red blood cell production. This drug, (Sotatercept) is currently in clinical trials for stimulating red cell production in people receiving chemotherapy, so there is a growing body of data on its pharmacological properties and toxicities in humans. This will be a very fascinating trail to watch.

Ms. Sara Sjöfgren (Sweden) presented data of applying a "big Pharma" approach to DBA drug discovery. She is working in the laboratory of Dr. Johan Flygare where they are developing a high throughput approach to screen thousands of chemicals for their ability to rescue phenotypes

in a mouse cellular model of DBA. The success of high throughput approaches to drug development depends highly on the nature of the screen designed. Much effort is going into the initial design of their screen, which could have big payoffs once the system gets rolling.

While we still await breakthroughs on the clinical front, these talks indicate that progress is being made in translating basic science discoveries to the clinic.

The session on "**Basic Mechanisms and Translation"** also provided insight into new avenues for drug development.

Dr. Allison Taylor (Boston) provided data on a screen for chemicals that could reverse some of the DBA-like phenotypes in their zebrafish model of DBA. Fewer chemical were tested that those proposed by the Flygare lab, but nevertheless encouraging results were presented. Dr. Taylor hit upon a drug which targets a signaling pathway which to this point was not known to be involved in DBA pathophysiology. I'm sure this discovery with stimulate related work in other models to see how well these results from zebrafish translate into mammalian systems.

Talks by Teng Teng (Cincinnati), Alan Warren (United Kingdom), Pierre-Emmanuel Gleizes (France) and Fabrizio Loreni (Italy) highlighted the complexity of signaling pathways linking p53 activation to ribosome stress. This complexity may ultimately be to our benefit as it may present more opportunities for targeting p53 related pathways without an associated cancer risk. More work in this area was presented in posters from Akiko Shimamura (Seattle) and Nadia Danilova (California).

In addition to their relative importance in drug development, it is worth noting that the mechanisms through which ribosome stress signals to cell growth and death decisions have been known for some time to play a role in carcinogenesis. Dr. Adrianna Vlachos (New York) gave a talk on their analysis of cancer incidence in patients within the North American DBA Registry (DBAR). While there appears to be an increased incidence of cancer in DBA patients compared to the general population, the risk of cancer in DBA does not appear to be as great as with several other bone marrow failure syndromes. The question on many people's minds at the meeting is whether the ribosome stress underlying most cases of DBA creates a selective pressure to overcome this stress by altering these signaling pathways, which in turn would put a patient at risk for cancer. This is a very active area of investigation on both the DBA and the cancer fronts. Two posters on clinical characteristics of DBA patients were also presented. The general characteristics through surveillance of DBA patients within the United States were presented in a poster from a Center for Disease Control (CDC) project conducted by Dr. Bert Glader (California) and Dr. Zora Rogers (Texas) while Dr. John Fargo (National Cancer Institute) presented a poster on the utility of adenosine deaminase measurements in DBA diagnosis.

Another topic raised in this session on basic mechanisms, was whether heme toxicity has a role in DBA pathophysiology. Dr. Janice Abkowitz (Seattle) presented her work on a heme transporter, which in mouse models gives rise to a phenotype very much like DBA. Her work on alterations in heme metabolism during erythroid development promises to shed new light on her intriguing proposal. Dr. Chetankumar Tailor and his student, Francisca Aidoo, Msc (Toronto) presented two posters that tied into a potential role for this heme transporter in DBA. Their work suggests that ribosomal protein haploinsufficiency may alter the splicing pattern of this transporter's mRNA thereby altering its expression. Other potential targets downstream of

ribosomal protein haploinsufficiency were presented in posters by Dr. Marieke von Linderd (The Neatherlands), Irma Dianzani (Italy), Elena Bibikova (California), and Sarah Bray (Australia).

A last topic in this session was covered by Dr. Lingbo Zhang (Boston) who identified a new protein required for the ability of glucocorticoids to stimulate erythropoiesis. The identification of the mechanisms through which glucocorticoids influence erythropoiesis opens the door for the development of new, less toxic drugs targeting this pathway. Dr. Leighton Grimes (Cincinnati) presented a poster on his work on targeting microRNAs in leukemia. Many questions were raised regarding the potential for targeting these RNAs as a therapy for DBA.

As I hope you can tell from this discussion the session on basic mechanisms provided considerable food for thought for future drug development.

Arguably the most progress in DBA research of the past few years has been in gene discovery. This work was highlighted in the session on **"DBA Genetics"**. Dr. Elizabeth Chao, Medical Director, Ambry Genetics presented a poster from Ambry Genetics indicating that they are now routinely screening DBA patients for mutations in 11 different ribosomal protein genes in a cost effective manner. Despite this progress these genes only represent approximately half of the genes affected in DBA patients. Several large scale gene discovery projects were reported at the meeting. Dr. Jason Farrar (Baltimore) presented his work on scanning whole genomes of DBA patients for large deletions. Genes affected by these large genes cannot be readily detected by traditional DNA sequencing technology. These studies indicated that a relatively high percentage of DBA patients have these relatively large deletions. Consequently, companies like Ambry Genetics will need to expand their genetic analyses in DBA patients to include deletion testing. Support for this view, also came from a poster from Dr. Paola Quarello (Italy) on her analysis of large deletions in patients in the Italian DBA Registry. Dr. Adrianna Vlachos (New York) highlighted the importance of deletion analysis by identifying a patient within the DBA Registry that had a specific deletion and non-classical form of DBA that responded to an alternative therapy. Dr. Marcin Wlodarski (Germany) also presented his large scale gene discovery work on patients within the German DBA Registry.

Dr. Hanna Gazda (Boston) presented work using whole exome sequencing to interrogate genes in DBA patients. Whole exome sequencing refers to sequencing only expressed genes rather than sequencing the whole genome, which is nevertheless a considerable effort. She was rewarded for this effort by the identification of the first non-ribosomal protein gene involved in DBA. Whether this represents a new subtype of DBA or whether this new gene somehow ties into ribosomal protein haploinsufficiency must await further studies.

In addition to the genes responsible for DBA, we are now in a position to begin to address so called modifier genes, which influence how DBA presents and responds to therapy in one patient relative to another. Dr. Anna Rita Migliaccio (New York) presented her work on polymorphisms in the glucocorticoid receptor gene. The big question here for DBA is whether these changes in the glucocorticoid gene in the human population possibly affect the response to steroids in DBA patients.

Variability in clinical presentation was also discussed by Dr. Lydie DaCosta (France) and Dr. Johnson Liu (New York) in a session on developmental biology. Dr. Liu used mouse embryonic stem cell models of DBA to show that deletions of different ribosomal proteins had different effects on stem cell differentiation. These studies indicate that the heterogeneity in clinical

presentation in DBA may be linked in part to the gene affected. Dr. DaCosta provided some of the first genetically conclusive evidence that DBA can present during fetal development. These studies indicate that DBA should be considered in the differential diagnosis of fetal anemia. They also raised the question of why the developmental timing of DBA differs between patients.

The meeting's plenary session was two talks on **"Assessment of iron loading in Diamond Blackfan anemia"**. This session was particularly timely given the recent deaths in the DBA community linked to complications of iron overload. Dr. Ellis Neufeld (Boston) spoke on the different iron chelation therapies currently available both in the US and Europe. He indicated that neither of these therapies were totally adequate and presented work on a new chelation therapy currently under development. Dr. Thomas Coates (California) gave a talk that made the very strong point that serum ferritin is a totally inadequate way to monitor tissue iron. He provided evidence that different tissues take up iron by different mechanisms and different rates, and that a single measure like serum ferritin simply cannot effectively monitor tissue iron loading. His point was re-enforced by Dr. Josu de la Fuente (London) who showed evidence of tissue iron overload in DBA patients despite their maintaining serum ferritin within an acceptable range. Numerous participants at the meeting commented in their evaluations that more work needs to be done in the area of iron loading in DBA patients.

It seems fitting in this synopsis of the 12th Diamond Blackfan Anemia International Consensus Conference that I end with what this conference was all about. Ms. Marie Arturi began the conference by emphasizing the while the scientific progress in DBA research over the past few years nothing short of remarkable it is of the utmost importance that these discoveries be translated into more effective treatments for DBA patients. Her point was brought home in a moving presentation by Mr. Jeff Bond who along with his wife Jessica began the Captain Courageous Foundation in Australia after learning of their son Angus' DBA diagnosis. I think we can all take heart from this meeting that the pace of translating basic science to the clinic appears to be speeding up, so patients like Angus can have a much brighter future.

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